Chemotherapy-induced nausea and vomiting: A narrative review to inform dietetics practice

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) are common nutrition-impact symptoms experienced by cancer patients. They exert a detrimental effect on dietary intake, risk of malnutrition and quality of life. While CINV are primarily managed with medication, dietitians play an important role in the management of CINV-related complications such as reduced dietary intake. This review discusses the burden of nausea and vomiting which cancer patients can experience, including its effect on quality of life, nutrition status, and treatment outcomes. Implications for dietetic practice include the need to explore the nature of reported symptoms, identify predisposing risk factors, and to consider the use of a variety of interventions that are individualised to the patient's symptoms. There are little clinical data regarding effective dietetic interventions for nausea and vomiting. In summary, this review discusses dietetic-related issues surrounding CINV including the pathophysiology, risk factors, prevalence, and both pharmacological and dietetic treatment options.

Introduction

There are multiple chemotherapy agents that can induce nausea and vomiting. However, with the advent of modern anti-emetics, there has been a significant reduction in the prevalence of vomiting, with a current estimated incidence of less than 20%.[1, 2] Efforts to control nausea in this setting have been less effective, with up to 60% of patients reporting nausea despite the use of anti-emetic medication.[1] Consequently, nausea remains one of the most distressing side effects experienced by cancer patients, while vomiting is now of less concern.[3-5] In addition, research has consistently associated chemotherapy-induced nausea and vomiting (CINV) with adverse effects on dietary intake, risk of malnutrition and quality of life (QoL).[6, 7]

Dietitians routinely consult with cancer patients experiencing CINV and related symptoms. The aim of this manuscript is to inform dietetic practice by providing a general overview of CINV, as well as CINV-specific issues related to clinical nutrition. These include the pathophysiology, and management options for CINV, including current medications and potential dietetic treatment options.

Methods

A literature search was undertaken between January and July 2015 using the following databases: Medline, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library. Search terms were not limited by timeframe; instead, all searches were from the date of each database's inception until July 2015.The bibliographies of relevant articles were scanned to identify additional articles of interest. The evidence-based guidelines of the Academy of Nutrition and Dietetics, Dietetics Association of Australia and the Practice-based Evidence in Nutrition Knowledge Pathway were reviewed for additional

references. The following search terms were used: (Chemotherapy AND (nausea OR vomiting OR CINV)) AND ((Risk factors OR prognostic OR predictor) OR (Mechanism OR pathophysiology OR physiopathology) OR (Nutrition OR malnutrition OR weight) OR "Quality of life" OR guidelines OR ginger OR protein OR (CAM OR Complementary OR Alternative)). Only studies published in English with human subjects were included. The results of this search strategy are detailed in Figure 1 and include the following citations:[1-67]. The results of the literature search were sorted based on the headings included in this review and were used to inform the discussion of each topic.

Defining chemotherapy-induced nausea and vomiting

CINV is a collective term used to describe the presentation of nausea, vomiting or a combination of both symptoms associated with the administration of cytotoxic chemotherapy. While nausea and vomiting are related concepts, they involve distinct physiological mechanisms and are therefore defined separately in Table 1.[68]

Nausea is a subjective sensation of discomfort, typically associated with the epigastrium, which might result in vomiting. Due to this subjective nature, the sensation, location, duration and intensity of nausea reported by patients can vary.[30] In addition, multiple nutrition impact symptoms interlink with nausea such as appetite loss, lack of energy, taste changes and pain.[31] Hence, if a patient experiences nausea, it is prudent to investigate the individual's sensations in order to effectively target treatment towards those symptoms.

CINV is further classified as *acute*, *delayed*, *anticipatory*, *breakthrough*, and *refractory*. Exact definitions of *acute CINV* vary but it is generally considered to be nausea and/or vomiting that occurs within 24 hours of chemotherapy administration.[32] *Delayed CINV* is defined as nausea and/or vomiting that occurs after the first 24 hours post-chemotherapy.[68]

While this distinction might appear arbitrary, research suggests that differing physiological processes are involved in the acute phase when compared to the delayed phase.[69]

Anticipatory CINV is a conditioned response that occurs after previous cycles of chemotherapy in which nausea and/or vomiting were not adequately controlled. The current understanding of anticipatory CINV is explained in Pavlovian terms. According to this framework, a neutral stimulus (e.g. the smell of the hospital, the sight of treating staff) is coupled with an unconditioned response (CINV), caused by the unconditioned stimuli (chemotherapy). Once this occurs, a conditioned response develops wherein the formerly neutral stimulus elicits the same response as the unconditioned stimulus.[33] While a conditioning period is required for this coupling to occur, the length of this period varies according to the individual and can occur as soon as the second cycle of chemotherapy. Anticipatory CINV may also cause of certain food aversions, as food eaten during the days surrounding chemotherapy can be mentally paired with the sensation of nausea.

Breakthrough CINV is nausea and/or vomiting that occurs despite adherence to optimal anti-emetic protocols and is treated by administering additional "rescue" anti-emetic medication.[34] *Refractory CINV* comprises symptoms that occur in subsequent cycles despite delivery of optimal anti-emetic control in previous cycles.[34] If this occurs, additional medication is likely to be required.

Risk factors

An individual's risk of developing CINV is influenced by numerous factors (Table 2), which can be categorised into four broad categories: previous experience with nauseating stimuli (e.g. previous history of motion or morning sickness); genetic and trait factors (e.g. age and gender); psychosocial factors (e.g. anxiety); and finally, medical and treatment-related factors (e.g. dose, type of chemotherapy). The primary determinant of a patient's risk of

experiencing CINV is the emetogenic potential of the chemotherapy regimen. In order to guide anti-emetic therapy, chemotherapy regimens are stratified into the following classifications based on their emetogenic potential: minimally, fewer than 10% at risk; low , 10% to 30% of patients at risk; moderately, 30% to 90% of patients at risk; and highly emetogenic chemotherapy regimens, nearly all patients (> 90%) at risk.[34, 71]

Individual risk factors are associated with different levels of risk. For example, Molassiotis et al.[35] reported that patients with a history of nausea and vomiting (e.g. morning or motion sickness) were three times more likely to experience CINV (OR 3.2 , 95% CI: 1.29–7.95), while the odds of experiencing CINV increased by 69% for each incremental increase in reported pain (OR 1.69, 95% CI: 1.03–2.77). Patients with a greater number of these risk factors are more likely to experience CINV compared to patients with fewer traits. This has led to the development of multiple tools designed to predict the risk of CINV by assessing the cumulative effect of risk factors. For example, Bouganim et al.'s[36] tool to predict CINV risk demonstrated that patients categorized as at high-risk of CINV were three times more likely to experience symptoms than patients who were considered to be low risk. Predictive tools such as this are currently being refined and validated in larger populations, but with further studies these tools could improve symptom control by helping to identify high-risk patients before chemotherapy begins.

Pathophysiology

The development of CINV is complex; this section briefly describes the pathophysiology in CINV development.

The trigger site for CINV is thought to be within the gastrointestinal tract. Chemotherapy agents can directly interact with enterochromaffin cells located within the gastric epithelium, resulting in the release of the neurotransmitters serotonin and substance *P*.[75] The released

neurotransmitters then interact with receptors located upon the vagus nerve, which subsequently transmits afferent signals to the chemoreceptor receptor zone (CTZ), a section of the brain within the area postrema, via the nucleus tractus solitarius. It is thought that modern 5-HT_3 antagonist medications (e.g. ondansetron) interact with the 5-HT_3 receptors involved in this process, which then mitigates the degree of afferent vagal signalling. Another neurotransmitter, substance *P*, is also implicated in the generation of CINV primarily by binding to NK_1 receptors located centrally within the brain. Stimuli transmitted using these two neuropeptides, as well as stimuli from other neurotransmitters (e.g. dopamine, histamine) and other regions of the brain (e.g. the amygdala), are processed by the CTZ and vomiting centre, which then coordinate the relevant musculature to induce a nausea and/or vomiting response.[76]

An additional source of afferent signalling is suggested to be via direct interaction with the area postrema, as this part of the brain has a semi-permeable membrane that enables direct interaction with emetic stimuli within the blood or cerebrospinal fluid.

Impact on patient

Nutrition status

Malnutrition is both a serious and prevalent concern within the oncology setting.[44] Estimates vary but between 30-50% of the general oncology population experience malnutrition and has been reported to be as high as 88% in certain populations (i.e. head and neck cancer patients).[45-47] Malnutrition is considered an independent risk factor for mortality, increased length of stay, secondary infections, and healthcare costs.[44, 48, 49] Patients who experience CINV are particularly susceptible to malnutrition due to the direct effect of nausea and vomiting (e.g. the expulsion of food) or through behavioural factors (such as avoiding certain foods in an effort to prevent future bouts of CINV). Furthermore, vomiting can impede accurate nutrition diagnoses as it can reduce the validity of recorded dietary intake. Both

nausea and vomiting are considered nutrition impact symptoms that can result in malnutrition.[50-53] Cross-sectional and prospective studies investigating the effect of CINV on a patient's risk of malnutrition have reported a significant link.[7, 54]

For example, in a cross-sectional study of cancer patients undergoing chemotherapy (N=121), CINV was associated with malnutrition, as assessed using the Patient Generated-Subjective Global Assessment, demonstrating that the majority of patients with severe CINV were malnourished.[7] Similarly, in a prospective study including 104 chemotherapy patients, patients that experienced severe acute (mean: 5 vs 8; p=0.003) and delayed nausea (mean: 5.1 vs 8; p=0.017) were associated with higher PG-SGA scores compared to patients who experienced less severe or no nausea. .[54] However, the authors of this study noted that the anti-emetic regimens prescribed to patients within this study were not congruent with current guidelines. Therefore, while the observed prevalence might reflect typical clinical practice, the incidence and severity of CINV within this cohort could be higher than what might be observed if current anti-emetic recommendations were implemented.

When weight loss was measured instead of malnutrition, similar associations were identified. In a retrospective analysis of cachectic patients with pancreatic cancer (N=107), the absence of nausea and vomiting was an independent determinant of weight stabilisation (OR 6.5, 95% CI: 1.6-27.2; p=0.010).[29] Another study in a mixed oncology population (N=254) found that the prevalence of vomiting was higher in patients that experienced significant weight loss (>5% usual body weight) compared to patients that experienced minimal weight loss(32% vs 14%, respectively; p=0.005).[55]

In summary, while few studies have purposely investigated the association between CINV and malnutrition, the existing literature is consistent in its support of this association. In

particular, these studies suggest that in patients who experience CINV, nutritional status should be actively monitored and managed in order to reduce the risk of malnutrition.

Quality of life (QoL)

QoL is poorer amongst patients who experience CINV, either during the acute or delayed phase, compared to patients without these symptoms.[27, 28] Highly emetogenic chemotherapy regimens are more likely to reduce QoL than moderately- or low emetogenic regimens. This detrimental effect on QoL is exacerbated with each additional day of CINV and is often compounded as treatment progresses, because patients who experience CINV in their initial cycle of chemotherapy are more likely to report poorer CINV-related QoL in subsequent cycles.[27, 56] This indicates that the burden of CINV might be cumulative and affects future chemotherapy cycles if not adequately controlled during the first cycle.[25, 77] When nausea and vomiting are measured separately, the adverse effect of nausea on QoL has been reported to be greater than the effect of vomiting, which is particularly pertinent as the prevalence of nausea is higher when compared to vomiting.[57] This difference in effect on QoL is likely due to current antiemetic therapy being predominantly effective for controlling vomiting as compared to nausea.

Physical function

Uncontrolled CINV can lead to a number of potentially serious physical conditions and CINV-related hospital admissions. Due to the loss of potassium, sodium, chloride and water resulting from frequent or severe vomiting, CINV might result in dehydration, electrolyte disturbances, and acid-base imbalances.[24] Another concern is the risk of aspiration pneumonia, a condition where vomitus enters the bronchial tree, resulting in pneumonitis. This can lead to further complications and in some cases is fatal.[24] In severe cases of vomiting, oesophageal tearing and related bleeding and pain can occur. Nutritional deficiencies are also a potential issue due to inadequate dietary intake of nutrients secondary

to nausea and the inability to digest consumed food due to vomiting. These conditions can be further exacerbated by additional comorbidities.[58] Finally, during the 1980s, CINV-related treatment termination was reported to occur in patients;[23] however, it is likely that the prevalence of CINV-related treatment termination has been significantly reduced due to the improvement in anti-emetic medications.[22, 59]

Pharmacotherapy of CINV

Multiple medications prevent and relieve the distressing symptoms of CINV. International evidence-based guidelines, such as those developed by the Multinational Association for Supportive Care in Cancer and the National Comprehensive Cancer Network, suggest the ideal combination and timing of the available anti-emetics, according to the emetogenicity of the chemotherapy treatment.[34, 71] It is now common practice to include this standardised, combination approach to provide optimal control of CINV. While these medications are effective in reducing CINV, there is no single medication that offers complete protection during highly or moderately emetogenic regimens and therefore, the medications discussed below are administered in combination.[34]

5-HT_3 antagonists such as ondansetron, granisetron and palonosetron are important components of modern anti-emetic therapy. 5-HT_3 antagonists work by binding to the 5-HT_3 receptors within the gastrointestinal tract, which consequentially blocks afferent emetic signalling to the CTZ within the brain. Corticosteroids such as dexamethasone are used for their incidental anti-emetic attributes and are commonly prescribed in combination with other anti-emetics.[34] The mechanism of action for this class of drug is poorly understood but suggested mechanisms include the modulation of the capillary permeability of the CTZ, anti-inflammatory effects within the gastrointestinal tract, and the release of endorphins.[21] A relatively new class of anti-emetic medication is NK_1 antagonists such as aprepitant and fosaprepitant. These medications are believed to act centrally within the CTZ by inhibiting

the actions of the neuropeptide, substance *P*.[60] NK_1 antagonists are used in combination, usually with dexamethasone and a 5-HT_3 antagonist. They are most effective for moderate to highly emetogenic chemotherapy, especially where delayed CINV occurs. Until the introduction of 5-HT_3 antagonists, metoclopramide was one of the primary anti-emetic medications used to treat CINV. It has been suggested that metoclopramide, as with other dopamine antagonists such as phenothiazine and butyrophenone, primarily interacts with dopamine D2 receptors within the central nervous system, eliciting a prokinetic effect on the gut and therefore regulating gut mobility. However, due to the superiority of the new generation of anti-emetic therapy and the incidence of extrapyramidal reactions with high-dose metoclopramide, anti-emetic guidelines only recommend metoclopramide for low emetogenic regimens and as a rescue anti-emetic in breakthrough emesis.[34, 71]

Dietetic and lifestyle interventions

Dietetic-related interventions

Dietitians regularly recommend a number of strategies to help patients manage their nausea and vomiting during chemotherapy. Broadly, these are categorised as strategies that involve modification to meal types and/or composition, behavioural strategies that target the way food is consumed, and lifestyle or environmental strategies (Table 3).[78-80] While many of these strategies appear intuitive, there are currently no clinical trials that have specifically investigated the efficacy of these strategies in reducing measures of CINV. Furthermore, while there are guidelines for the dietetic management of CINV,[80, 81] the lack of clinical trials means that these guidelines largely rely on expert opinion. However, medical nutrition therapy (MNT) is an intervention delivered by a dietitian that is tailored to the individual's need and circumstances and utilises the strategies outlined in table 3. Therefore, despite the lack of studies specifically investigating dietary interventions for CINV, studies investigating

MNT as an intervention may provide some evidence for the use of these strategies in the management of CINV.

[44, 82]The oncology guidelines of the Academy of Nutrition and Dietetics state that there is currently strong evidence that MNT improves multiple treatment outcomes in patients undergoing chemotherapy, radiation or chemoradiotherapy in ambulatory or outpatient and inpatient oncology settings.[82] However, when studies that have investigated the use of MNT in chemotherapy have been analysed separately from studies that have investigated MNT during radiotherapy, the evidence remains strong to suggest that MNT improves clinical and patient-centred outcomes (e.g. quality of life) in patients receiving radiotherapy but less so in patients receiving chemotherapy. Updated evidence-based practice guidelines endorsed by the Dietetic Association of Australia, state that evidence that MNT during chemotherapy results in similar improvements in clinical or patient-centred outcomes is currently insufficient.[44] The authors of these guidelines found that while dietary supplements or simple dietary interventions (e.g. provision of handouts detailing food high protein and energy or basic nutrition counselling) were able to improve nutritional outcomes such as dietary intake and weight status, they did not find an improvement in quality of life or survival.

There is preliminary support for the use of MNT as part of CINV management. In a small study (N=35) of ambulatory cancer patients, nausea modestly improved after a two month multidisciplinary intervention involving a dietitian as well as a physical therapist, social worker, nurse, and a physician (no *p* value reported).[20] Furthermore, two randomized controlled trials that investigated the use of dietary counselling or nutrition supplements in colorectal and head and neck cancer patients undergoing radiotherapy found that the severity and incidence of CINV was reduced within participants who received dietary counselling.[19, 61] While this was in a population undergoing radiotherapy, the pathways involved in the generation of nausea and vomiting are thought to be similar to CINV. These studies therefore

provide preliminary support for the use of dietary counselling for these symptoms. Further studies are required to investigate the use of MNT during chemotherapy to manage CINV and assess the effect on clinical outcomes such as survival, length of stay and QoL.

There is limited evidence that CINV is associated with taste changes. One study found that patients who reported experiencing CINV also reported greater levels of taste changes and metallic taste.[18] The nature of this relationship has not been elucidated, so it is unclear if the use of MNT to manage taste changes may also provide relief to nausea and vomiting symptoms.

Protein-rich meal consumption

Preliminary clinical data suggest the consumption of a mixed meal, and in particular, a protein-rich meal, might improve nausea and vomiting symptoms from a variety of nauseating stimuli, including chemotherapy. For example, a prospective study (N=143) reported that patients who did not consume food before chemotherapy were 6.8 times more likely to experience CINV compared to patients who reported eating meals prior to chemotherapy.[57] Jednak et al.[62] examined this effect further in a clinical trial that investigated the effect of different macronutrients on nausea during pregnancy. The results indicated that a protein-rich meal significantly reduced nausea symptoms compared to both equicaloric carbohydrate and fat meals, and non-caloric meals. Subsequently, Levine et al.[17] explored this in 28 cancer patients undergoing chemotherapy and reported that a combination of ginger and protein supplementation resulted in a significant reduction in CINV. This effect was more pronounced in the group receiving the highest dose of protein, which indicates that protein supplementation might have been primarily responsible for the reduction in CINV.

The exact mechanism for this is unclear but it has been observed that during exposure to nauseating stimuli, the electrical rhythm of the stomach becomes dysregulated.[17] The

ingestion of a meal maintains the normal physiological rhythm of the stomach, which might in turn reduce symptoms of nausea and vomiting. The observed superiority of protein in reducing nausea symptoms is attributed to its effect on gastrin secretion, which is believed to normalise gastric activity.[16] However, while the current evidence is supportive, further studies that include larger sample sizes are required, particularly in the chemotherapy setting.

Ginger supplementation

In vitro and animal research indicate that compounds within ginger might exert several effects on pathways relevant to CINV. These include 5-HT_3 receptor antagonism and the modulation of gastrointestinal motility and gastric emptying rate.[14] In a recent systematic literature review, seven clinical trials were included that tested doses between 0.5-2g of ginger capsules.[15] The results provide equivocal evidence, with two studies reporting no effect,[13, 63] three finding some effect,[12, 64, 83] and two studies in favour but with caveats that reduce the real world application of these results.[10, 65] Our review also identified multiple limitations within the literature such as a lack of control for anticipatory nausea and prognostic factors that might influence individual CINV response, inconsistent use of standardized ginger formulations and validated questionnaires, and the use of potentially suboptimal dosing regimens. Hence, while some evidence supports ginger as an adjuvant anti-CINV therapy, existing limitations must be addressed before firm recommendations for its use can be made.

Additional complementary therapies

Several additional complementary therapies have demonstrated varying degrees of efficacy. These include yoga, progressive muscle relaxation, massage, aromatherapy, hypnosis, exercise, education programs, and acupuncture-point stimulation.[8, 9, 66, 67] However, while many of these therapies are likely to be low-cost and have minimal side effects, further trials

are required to address limitations within the literature such as small sample sizes and inconsistent results.

Conclusion

In summary, CINV poses a significant burden to patients undergoing chemotherapy with the potential to result in further medical complications, reduce QoL, and increase the risk of malnutrition. While some evidence of a benefit from dietary intervention using MNT or protein rich meals exists further research is required.

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